CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER for: 020702, S018

ADMINISTRATIVE DOCUMENTS and CORRESPONDENCE

Pharmaceutical Research
2800 Plymouth Road Phone: (734) 622-7000
Ann Arbor, MI
48105

PARKE-DAVIS

November 23, 1999

NDA 20-702
Ref. No. 102
Lipitor® (atorvastatin calcium) Tablets

Re. Amendment to Efficacy
Supplement – 018:
Revised Draft Labeling

Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine
Drug Products (HFD-510)
Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
Parklawn Building
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Sobel:

On behalf of, and as agent for Warner-Lambert Export, reference is made to our supplement (S-018), submitted on March 3, 1999 (Ref. No. 83), to our approved NDA 20-702 for Lipitor® (atorvastatin calcium) Tablets. This supplement supports the use of atorvastatin to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial) and mixed dyslipidemia (Fredrickson Type IIa and Type IIb). Reference is also made to a request made by Dr. Orloff of your Division on November 16, 1999 for additional changes in the revised draft labeling, submitted November 5, 1999 (Ref. No. 100). Reference is also made to our submission on November 17, 1999 (Ref. No. 101) of revised draft labeling reflecting Dr. Orloff's request of November 16, 1999. Reference is also made to a telephone conversation with Dr. Orloff on November 23, 1999 discussing his requested changes in our labeling. During this conversation, we agreed on a slight modification to the wording submitted in our November 17, 1999 amendment. As a result of this discussion and the agreements made, we are hereby submitting revised draft labeling for this efficacy supplement (Attachment 1).

The current revision of the draft label contains the following changes that were submitted on November 5, 1999. New text (underlined) has been added under the CLINICAL PHARMACOLOGY, Clinical Studies section on pages 4 and 5 of the revised draft labeling. In addition, the INDICATIONS AND USAGE section on pages 7 and 8 has been modified (current labeling text is shown with strike-through, new text is underlined).

As agreed during our November 23, 1999 teleconference, additional wording has been added under WARNINGS, Skeletal Muscle and PRECAUTIONS, Drug Interactions on page 11 of the revised draft labeling.

Should you have any questions regarding this submission, please contact me at 734/622-5225 or send a facsimile to 734/622-3283.

Sincerely,

Jeffrey Koup, Pharm.D.
Director, FDA Liaison
Worldwide Regulatory Affairs

Desk Copy: Dr. David Orloff (HFD-510)
Ms. Margaret Simoneau (HFD-510)

JK:kb
11-23-1999\RN-102\20-702\CI-0981\Letter

Attachment

APPEARS THIS WAY
ON ORIGINAL

ITEM 13.
PATENT AND MARKET EXCLUSIVITY INFORMATION

13.1. Patent Information

NDA Number:	20-702
Applicant:	Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company PO Box 1047 Ann Arbor, MI 48106
Active Ingredient:	[R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate
Medical Use:	Synthetic lipid-lowering agent
Strength:	10, 20, and 40 mg
Dosage Form:	Tablet
Trade Name:	Lipitor®
Generic Name:	Atorvastatin (calcium)
Patent Statement:	Four patents cover atorvastatin (calcium)

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Patent Statement:

US Patent Number:	4,681,893
Expiration Date:	September 24, 2009
Patent Type:	Compound per se Formulation
Assignee:	Warner-Lambert Company
US Patent Number:	5,273,995
Expiration Date:	December 28, 2010
Patent Type:	Compound per se Formulation
Assignee:	Warner-Lambert Company
US Patent Number:	5,385,929
Expiration Date:	May 4, 2014
Patent Type:	Compound per se Formulation
Assignee:	Warner-Lambert Company
US Patent Number:	5,686,104
Expiration Date:	November 11, 2014
Patent Type:	Formulation
Assignee:	Warner-Lambert Company

The undersigned declares that Patent Numbers 4,681,893; 5,273,995; 5,385,929; and 5,686,104 cover a formulation of atorvastatin calcium, which product is the subject of this application for which approval is sought

Francis J. Tinney 2-9-99

Francis J. Tinney
Senior Counsel
Pharmaceutical Patents

13.2. Request for Market Exclusivity

As provided for by 21 CFR 314.108(b)(4), Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, is requesting a 3-year period of market exclusivity for Lipitor® as an effective therapeutic option to decrease the non HDL-C/HDL-C ratio and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson types Iia and IIb). Parke-Davis certifies that the active moiety, atorvastatin calcium, meets the criteria for the exclusivity period specified in 21 CFR 314.50(j)(4) and in 21 USC 355(j)(4)(D)(iii) and 355(c)(3)(D)(iii), specifically:

1. No drug product containing atorvastatin calcium for the indication sought in this application has been previously approved.

2. New clinical investigations, other than bioavailability or bioequivalence studies, are being submitted to support this application. Parke-Davis certifies that this clinical study has not formed part of the basis of a finding of substantial evidence of effectiveness for a previously approved NDA.

3. a. Parke-Davis certifies that the company has thoroughly searched the scientific literature and, to the best of our knowledge, no published studies or publicly available reports of clinical investigations with atorvastatin calcium are relevant to support the indication sought in this application.

   b. Parke-Davis certifies that, in the applicant's opinion, the present application could not be approved without the new clinical investigations.

4. Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, is the sponsor named in the Form FDA 1571 for IND[ ]under which the clinical investigation identified in Item 2 above was conducted.

EXCLUSIVITY SUMMARY FOR NDA # 20-702 SUPPL # 18

Trade Name LIPITOR Generic Name ATORVASTATIN

Applicant Name PFIZER-DANIS HFD # 510

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /___/ NO /✓/

b) Is it an effectiveness supplement?

YES /✓/ NO /___/

If yes, what type? (SE1, SE2, etc.) SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /✓/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /✓/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

NO

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /✓/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

NA

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved.

Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /✓/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /✓/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /✓/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /✓/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /✓/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

data pooled from 24 previously submitted studies

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /✓/ not this specific subgroup

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /✓/ not for this subgroup

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

subgroups pooled from 24 previously submitted studies

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # [_____] YES /✓/ ! NO /___/ Explain: _____

! _____

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /✓/

If yes, explain: _____

_____

/S/ November 24, 1999

Signature Date

Title: Project Manager

/S/ 12-2-99

Signature of Office/ Date
Division Director

cc: Original NDA Division File HFD-85 Mary Ann Holovac

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

IBLA # 20-702 Supplement # 18 Circle one (SE1) SE2 SE3 SE4 SE5 SE6

.r___ Trade and generic names/dosage form: Lipitor (atorvastatin) Action: (AP) AE NA

Applicant Parke Davis Therapeutic Class Lipid altering

Indication(s) previously approved to reduce total C, LDL-C, ApoB, and TG levels in pts w primary hyperchol + mixed dyslipidemia + for treatment of Fredrickson Types IV + V + III

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ✓

Proposed indication in this application adds indication of ↑ HDL-C in pts w primary hypercholesterolemia (beta Lam + non-fam); mixed dyslipidemia (Fred Type 2a + 2b).

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ✓ Yes (Continue with questions) ___ No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

___ Neonates (Birth-1month) ___ Infants (1month-2yrs) ___ Children (2-12yrs) ✓ Adolecents(12-16yrs)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

✓ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

✓ c. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing.

___ (2) Protocols were submitted and approved.

✓ (3) Protocols were submitted and are under review.

___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply, attach an explanation, as necessary.**

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___ Yes ✓ No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from Med. Team Leader (e.g., medical review, medical officer, team leader)

/S/ (Team Leader) 11-19-99

Signature of Preparer and Title Date

Orig NDA/BLA # 20-702
HFD-510 /Div File
NDA/BLA Action Package
HFD-006/ KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT YUYATI ROBERTS, HFD-5 /ROBERTSY